

## CHAPTER II

### HISTORY

#### 1. The chemical constituents of *Andrographis paniculata* Nees.

The chemical constituents of plant that were found in *Andrographis paniculata* Nees. They are lactone, flavonoids and miscellaneous, as shown in Table 1. and Figure 2.

**Table 1. The chemical constituents in *Andrographis paniculata* Nees.**

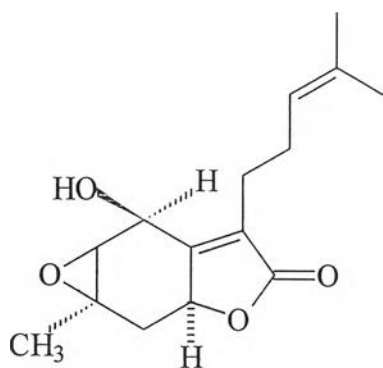
Category	Chemical compound	Plant part	Reference	
<b>Lactone</b>	Sesquiterpene	Paniculide A (1)	leaves, tissue culture	Allison, A.J. et al. 1968
	lactone	Paniculide B (2)		
		Paniculide C (3)		
	Diterpene lactone ( <i>ent</i> -labdane )	Andrographolide (4)	leaves, whole plant stem	Chakravarti, D. Chakravarti, R.N. 1982
		Deoxyandrographolide(5)	leaves	Balmain, A. and Connolly, J.D 1973
		14-deoxy-11,12-didehydro andrographolide (6)	whole plant	
		14-deoxy-11-oxoandrogra pholide (7)		
		Deoxyandrographoside (8)	leaves	Weiming, C. and xiaotian, L .1982
	Neoandrographolide (9)	leaves	Fujita, T. et al. 1984	

**Table 1. The chemical constituents in *Andrographis paniculata* Nees. (continued)**

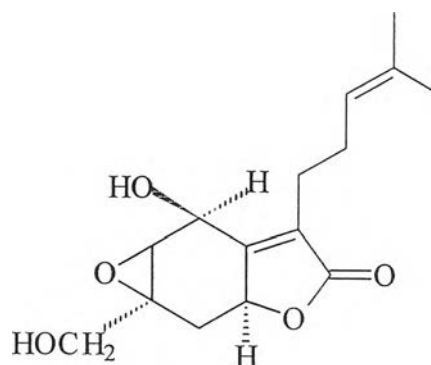
Category	Chemical compound	Plant part	Reference
Diterpene lactone ( <i>ent</i> -labdane)	Andrograpanin (10)	leaves	Fujita, T. et al 1984
	Andrographiside (11)	aerial parts	Takakuni, et al. 1994
	12- <i>epi</i> -14-deoxy-12-methoxy-an drographolide (12)		
	14-deoxy-12-methoxy-androgra pholide (13)		
	14-deoxy-11-hydroxy-androgra pholide (14)	aerial parts	
	14-deoxy-12-hydroxy-androgra pholide (15)		
	14-deoxy -11,12-didehydroan drographiside (16)		
	6'-acetylneoandrographolide (17)		
	14- <i>epi</i> -andrographolide (18)		
	Isoandrographolide (19)		
Diterpene dimers	Bisandrographolide A (20)	aerial parts	
	Bisandrographolide B (21)		
	Bisandrographolide C (22)		
	Bisandrographolide D (23)		
<b>Flavonoids</b>			
Flavone	Andrographin (24)	root	Biswas, Ali, and Choudhury. 1972
	Panicolin (25)		
	Mono- <i>o</i> -methyl-wightin (26)		
	Apigenin-4'-7'-di- <i>o</i> -methyl-ether (27)		

Table 1. The chemical constituents in *Andrographis paniculata* Nees.(continued)

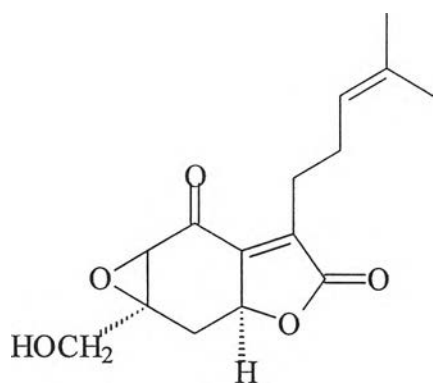
Category	Chemical compound	Plant part	Reference
<b>Flavonoids</b>	5-hydroxy-2',3',7,8-dimethoxy flavone (28)	root	Gupta, et al. 1983
	5-hydroxy-7,8-dimethoxy flavone (29)		
	(dl)-5-hydroxy-7,8-dimethoxy flavone (30)		
Flavone glucosides	Andrographidine B, C, D, E and F (31-35)	root	Kuroyanagi, et al 1987
Flavanone glucosides	Andrographidine A (36)		
<b>Miscellaneous</b>	2- <i>cis</i> ,6- <i>trans</i> -farnesol (37)	tissue culture	Overton, K.M and Robert, F.M1974
	2- <i>tran</i> ,6- <i>tran</i> -farnesol (38)		
	Caffeic acid (3,4-dihydroxy cinnamic acid ) (39)		Satyanarayana, D Mythirayee, C.and Krishna, M.1978
	Chlorogenic acid (40)	leaves	
	3,5-dicaffeoyl-d-quinic acid (41)		
	Potassium hydrogen phosphate (42)	whole plant	Gupta,S.et al1983



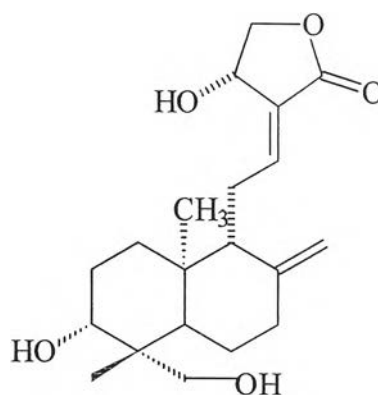
(1) Paniculide A



(2) Paniculide B

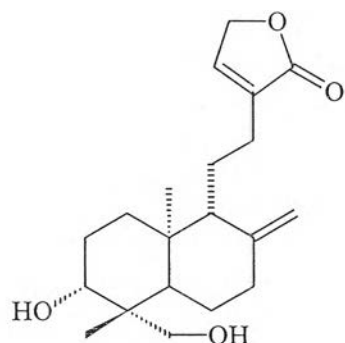


(3) Paniculide C

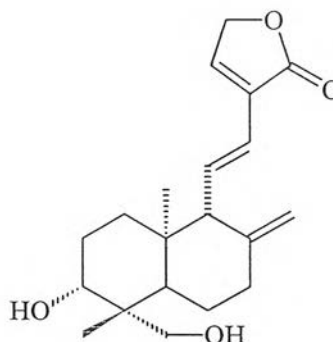


(4) Andrographolide

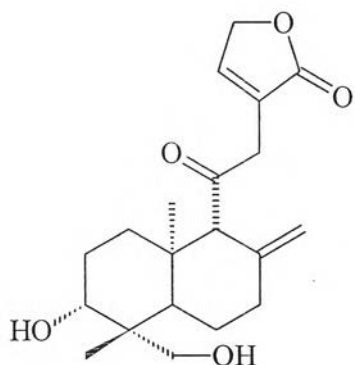
Figure 2. The chemical constituents of *Andrographis paniculata* Nees.



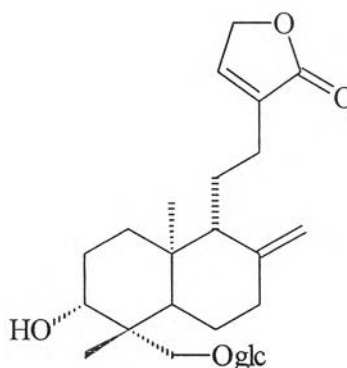
(5) Deoxyandrographolide



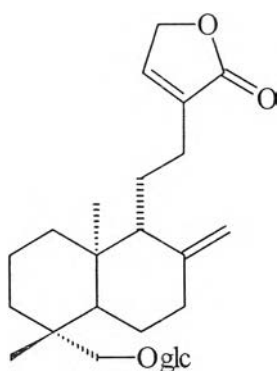
(6) 14-deoxy-11,12-didehydroandrographolide



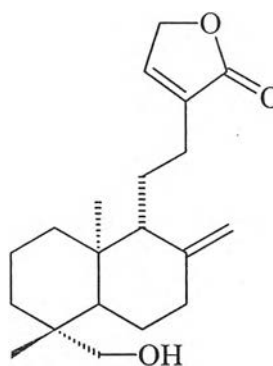
(7) 14-deoxy-11-oxoandrographolide



(8) Deoxyandrographoside



(9) Neoandrographolide



(10) Andrograpanin

Figure 2. The chemical constituents of *Andrographis paniculata* Nees.(continued )

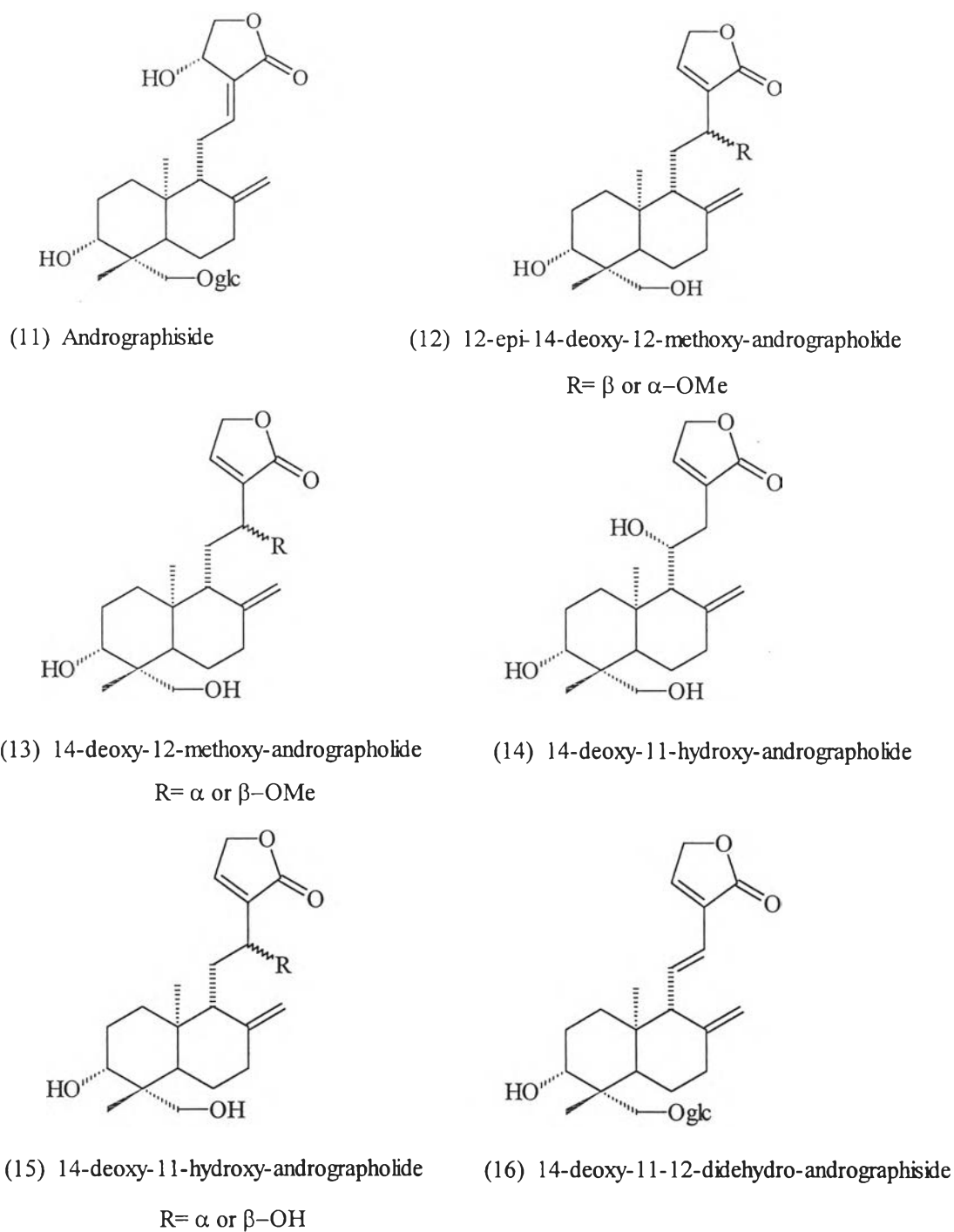
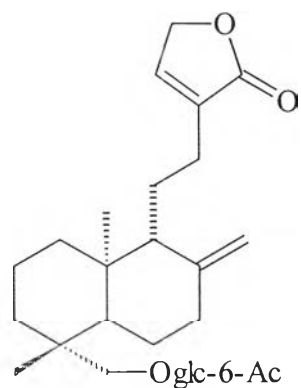
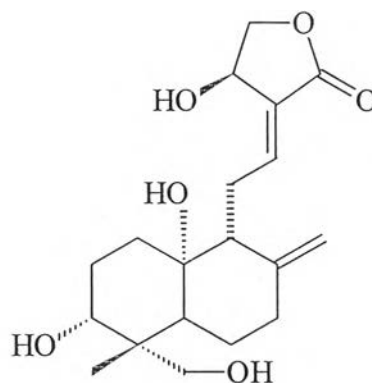


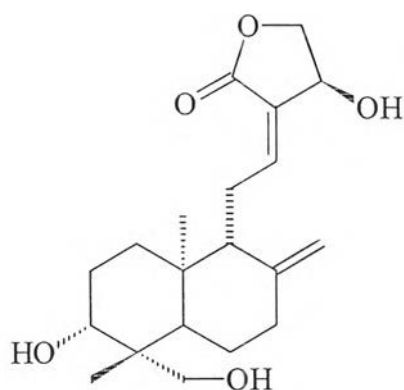
Figure 2. The chemical constituents of *Andrographis paniculata* Nees.(continued)



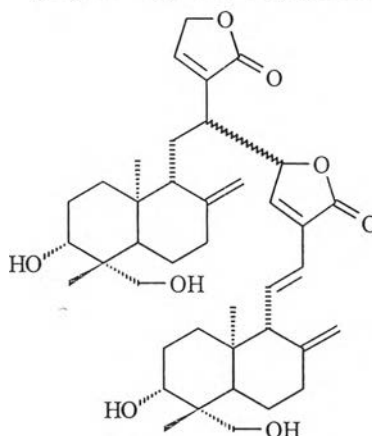
(17) 6' acetyneandrographolide



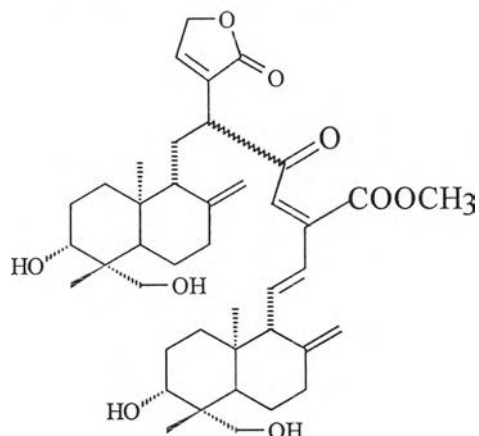
(18) 14-epi-andrographolide



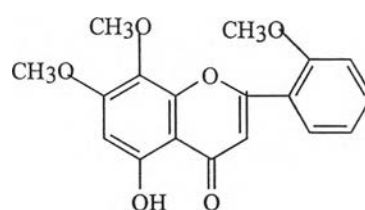
(19) Isoandrographolide



(20,21,22) Bisandrographolide A,B,C

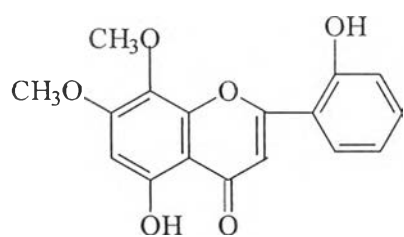


(23) Bisandrographolide D

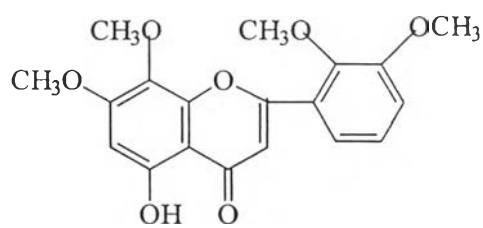


(24) Andrographin

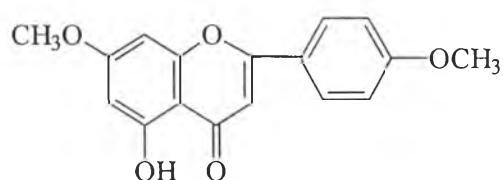
Figure 2. The chemical constituents of *Andrographis paniculata* Nees. (continued)



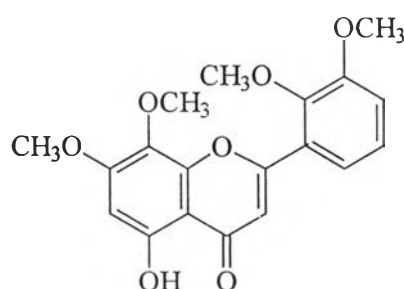
(25) Panicolin



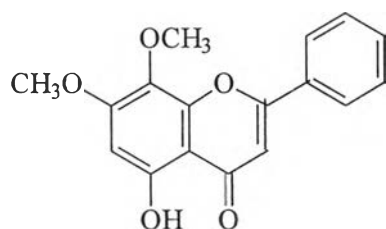
(26) Mono-o-Methyl-Wightin



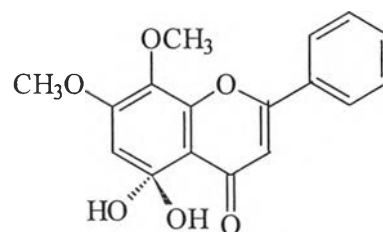
(27) Apigenin-4',7'-di-o-methyl ether



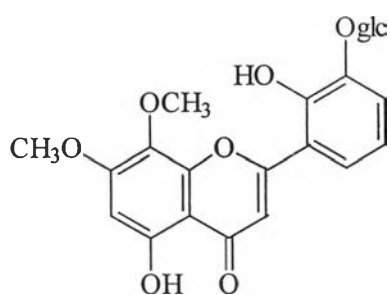
(28) 5-Hydroxy-2',3',7,8-tetramethoxyflavone



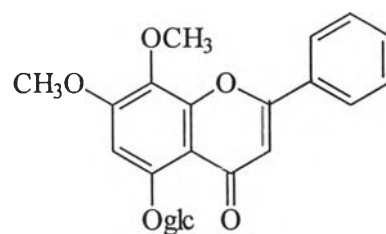
(29) 5-Hydroxy-7,8-dimethoxyflavone



(30) (dl)-5-Hydroxy-7,8-dimethoxyflavone



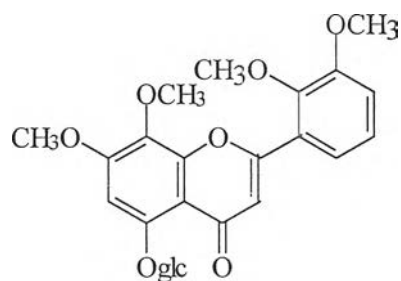
(31) Andrographidine B



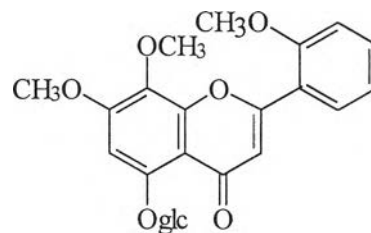
(32) Andrographidine C

Figure 2. The chemical constituents of *Andrographis paniculata* Nees.(continued)

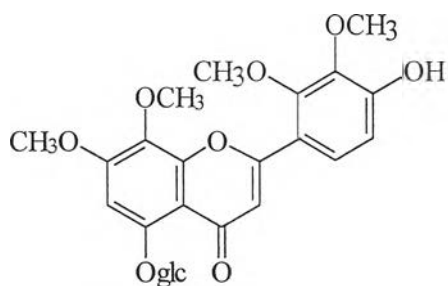




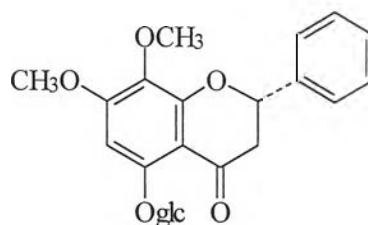
(33) Andrographidine D



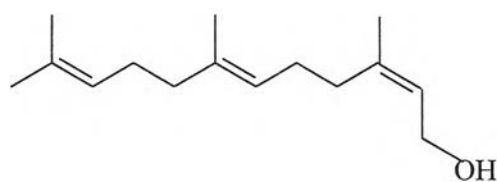
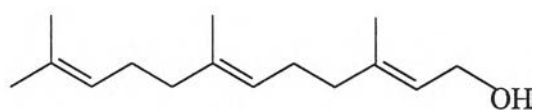
(34) Andrographidine E

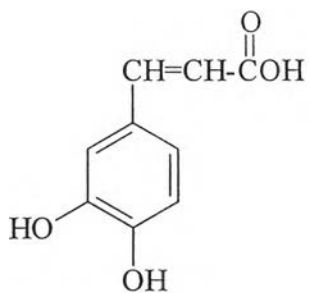


(35) Andrographidine F

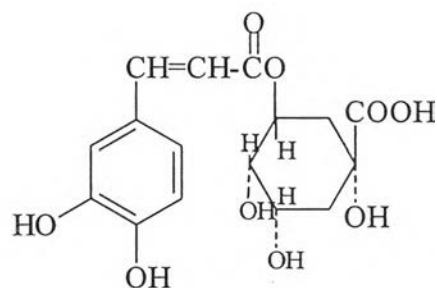


(36) Andrographidine A

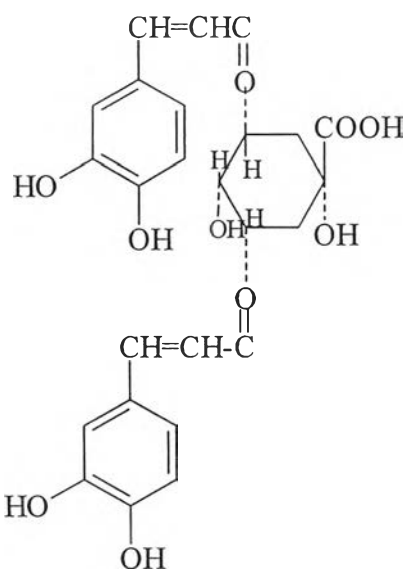
(37) 2-*cis*,6-*trans*-farnesol(38) 2-*trans*,6-*trans*-farnesolFigure 2. The chemical constituents of *Andrographis paniculata* Nees.(continued)



(39) Caffeic acid



(40) Chlorogenic acid



(41) 3,5-dicaffeoyl-d-quinic acid



(42) Potassium hydrogen phosphate

Figure 2. The chemical constituents of *Andrographis paniculata* Nees.(continued)

## 2. Naturally occurring terpenes

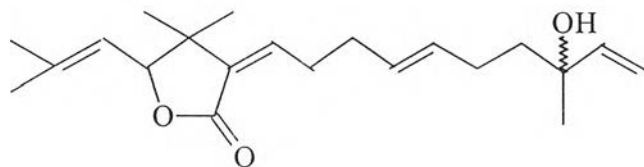
Terpenes are widely distributed in nature and are found in abundance in higher plants. In addition, fungi produce a range of interesting terpenes; marine organisms are prolific source of unusual terpenes, and terpenes are found as insect pheromones and insect defense secretions. Terpenes are defined as natural products whose structure may be divided into isoprene units. The isoprene units arise biogenetically from acetate via mevalonic acid and are branch-chain, five-carbon units containing two unsaturated units. During the formation of terpenes, the isoprene units are usually linked in a head to tail manner and the number of units incorporated into a particular unsaturated hydrocarbon terpenes serves as a basis for the classification of these compounds (James, E. Robbers. et al, 1996).

### 2.1 Diterpenes

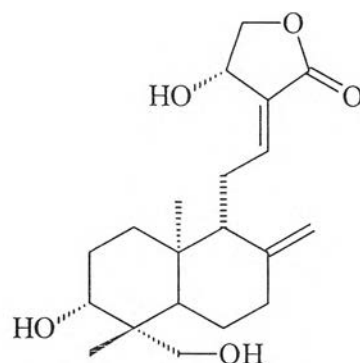
The diterpenes comprise a large group of non-volatile C<sub>20</sub> compounds derived from geranylgeranyl pyrophosphate. Although mainly of plant or fungi origin, they are also formed by some marine organisms and insects. In plant, **Forskin** or **Colforsin** in labdane diterpenes isolated from the roots of the Indian herb *Coleus forskohlii* (Poir.) Briq. (Fam. Lamiaceae). It was used in Hindu, Ayurvedic traditional medicine, as a novel class of drugs that activates cyclic AMP-generating system through an ability to stimulate adenylate cyclase in a receptor-independent manner. In addition, forskolin has a high therapeutic potential in congestive cardiomyopathy, bronchial asthma, glaucoma and hypertension. **Ginko** is a concentrated extract of the dried leaves of *Ginko biloba* Linne' (Fam. Ginkgoaceae) is currently a popular drug in Europe for treatment of peripheral vascular disease, particularly cerebral circulatory disturbance and other peripheral arterial circulatory disorders. **Taxol** or **Paclitaxel** is obtained from the bark of *Taxus brevifolia* Nutt. (Fam. Taxaceae). It is used in the treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy and in the treatment of breast cancer after failure of combination chemotherapy for metastatic disease (James, E. Robbers. et al, 1996).

**Diterpene lactone compounds** have been isolated from terrestrial of higher and lower plant and also marine natural source. There is no completely satisfactory classification of the diterpene lactones. The chemical structures of these compounds found in natural source are generally classified into 8 types (Srisomporn, P.1991). as follow (See figure 3 ):

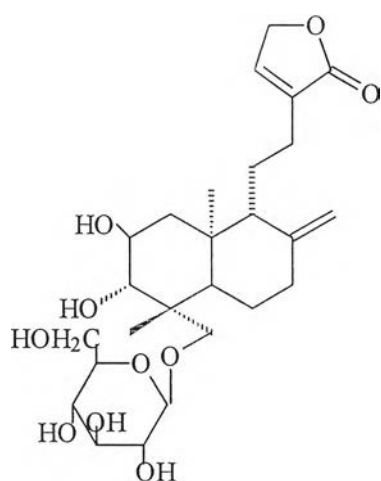
1. Phytane type diterpene lactone  
eg -Naviculide (43)
2. Labdane type diterpene lactone  
eg. -Andrographolide (4)  
-Phloganthoside (44)
3. Clerodane type diterpene lactone  
eg. -Scuterivulactone D (45)
4. Neoclerodane type diterpene lactone  
eg. -Sculellones E (46)
5. Diterpene furanolactone  
eg. -Jateorin (47)  
-Columbin (48)
6. Norditerpene lactone  
eg. -Picrodendron A (49)  
-Salignone (50)
7. Kaurane type diterpene lactone  
eg. -15-oxo-zoaplatin (51)
8. Miscellaneous  
eg. -Angasiol acetate (52)



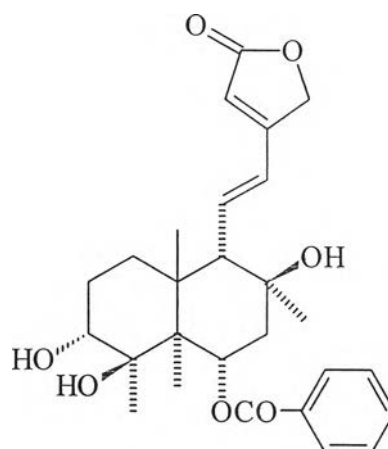
(43) Naviculide



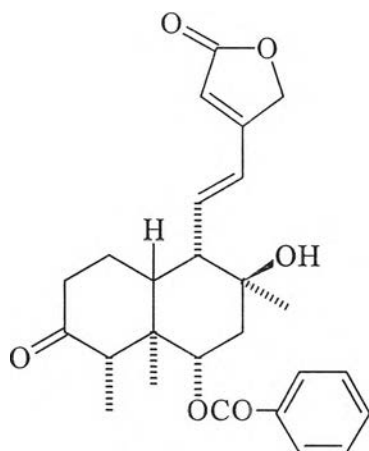
(4) Andrographolide



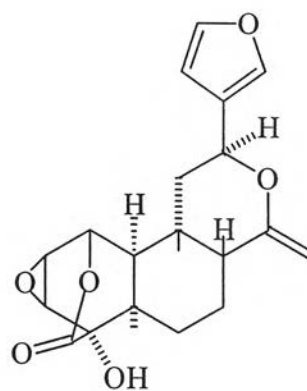
(44) Phloganthoside



(45) Scuterivulactone D

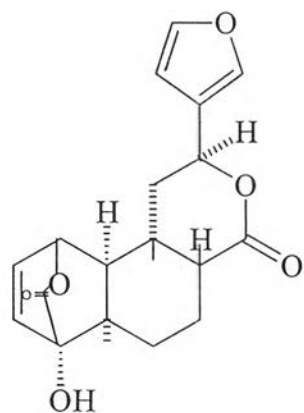


(46) Scutellone E

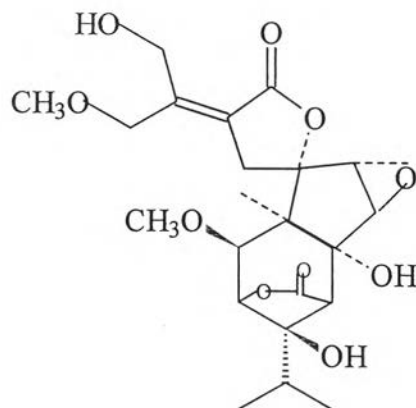


(47) Jateorin

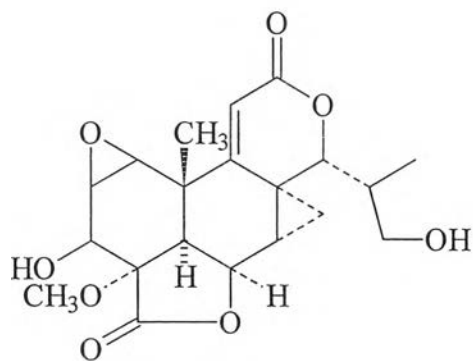
Figure 3. The chemical structures of some diterpene lactone compounds



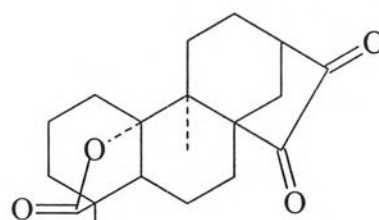
(48) Columbin



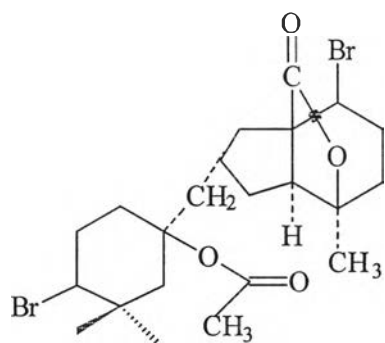
(49) Picrodendrin A



(50) Salignone



(51) 15-Oxo-zoaplatin



(52) Angasiol acetate

Figure 3. The chemical structures of some diterpene lactone compounds (continued )

### 3. Naturally occurring flavonoids

**Flavonoids** are among the most widely distributed natural product compounds in plants with over 2,000 different compounds reported occurring both in the free state and as glycosides. The flavonoid are structurally characterized as having two hydroxylated aromatic ring A and B joined by a three carbon fragment. The major general structure categories are flavones, flavanone, flavonols, anthocyanidins, and isoflavones. A variety of flavonoids have been assigned different roles in nature as antimicrobial compounds, stress metabolites, or signaling molecules.

The general biosynthesis of flavonoids involves the central intermediate  $p$ -coumaroyl CoA and three malonyl CoA units to elongate the side chain of the original phenylpropanoid unit (Harborne, J.B.et al, 1982).

### 4. Esterification of andrographolide and related diterpene lactone compounds

As already mentioned that the main components of this herb are the diterpene lactones of which andrographolide is the major component, that exact the interesting pharmacological action. The structure of andrographolide and of several minor related diterpene lactones have been recently deduced. It had been reported that the succinyl derivatives of andrographolide, dehydroandrographolide succinic acid monoester (DASM), can inhibit the growth of human immunodeficiency virus (HIV)in vitro. It was nontoxic to the human cell at the concentration of 50-200 (average,108)  $\mu\text{g/ml}$  (R, Shihman.Chang.et al 1991). Therefore, to reinvestigate, the previously data of Andrographolide and related diterpene lactone synthesized compounds (See figure 4):

1. Acetylation of Andrographolide (4) was prepared by

(Chakravarti,D. and Chakravarti R, M..1952)

-The enol lactone (53)

-14-deoxy-11,12-didehydroandrographolide diacetate (54)

-Triacetylandrographolide(55)

2. Diacetate(54)of Natural 14-deoxy-11,12-didehydroandrographolide(6)

(Cava,M P., W.R.Stein, R.P. and Willis, C.R.et al.1965 )

3. Neoandrographolide tetraacetate(56) (Siripong, P.et al 1992)

4.14-Deoxyandrographolide diacetate (57)( Cava, M. P. et al.1965 )

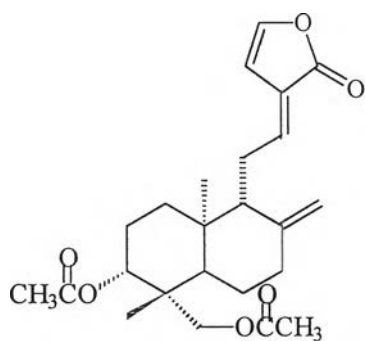
5. 14-Deoxy-11-oxoandrographolide diacetate (58) (Balmain, A.and  
Connolly, J.D.1973 )

6. Isoandrographolide diacetate (59) (Cava M, P. et al.1965 )

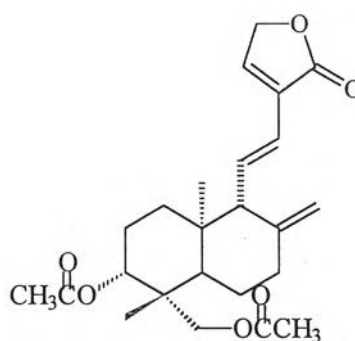
7. Dehydroandrographolide Succinic acid Monoester (R, Shihman  
Chang. et al.1991 )

-Dehydroandrographolide -3-monosuccinate (60)

-Dehydroandrographolide -19-monosuccinate (61)



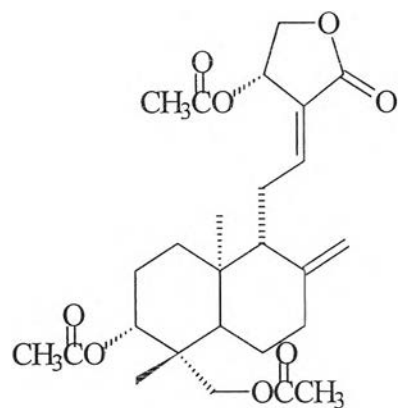
(53) The enol lactone



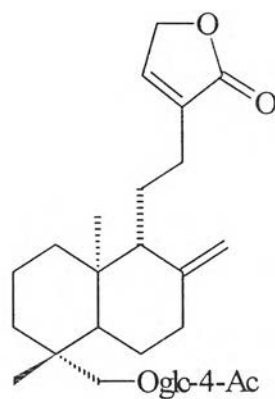
(54) 14-deoxy-11,12-didehydroandrographolide diacetate

Figure 4 The chemical structures of Andrographolide and related diterpene lactone synthesized compounds

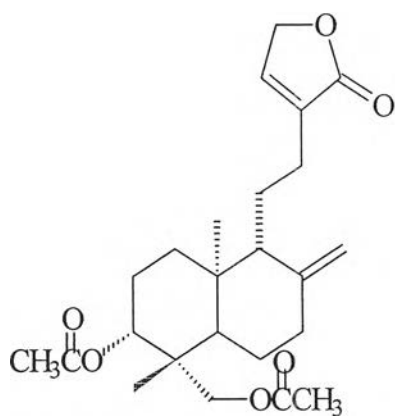




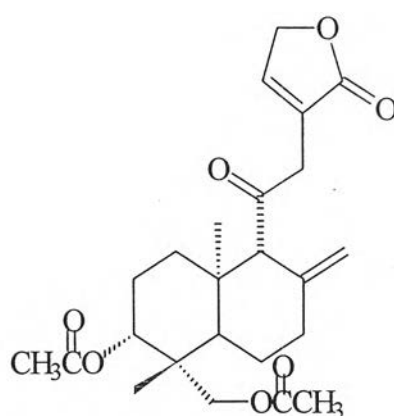
(55) Triacetylandrographolide



(56) Neoandrographolide tetraacetate

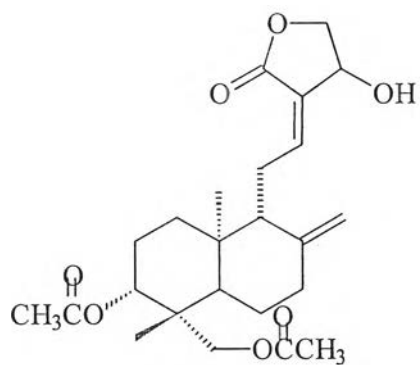


(57) 14-deoxyandrographolide diacetate

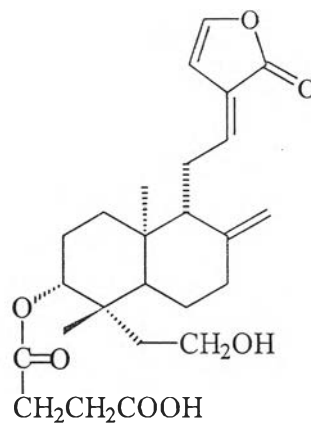


(58) 14-deoxy-11-oxoandrographolide diacetate

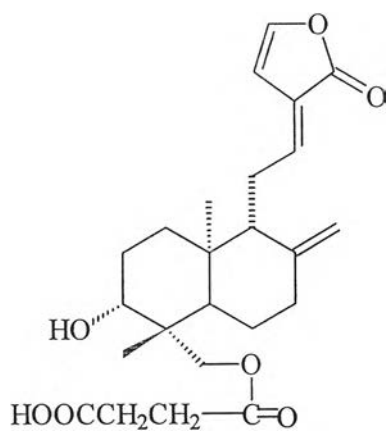
Figure 4. The chemical structures of Andrographolide and related diterpene lactone synthesized compounds (continued )



(59) Isoandrographolide diacetate



(60) Dehydroandrographolide monosuccinate



(61) Dehydroandrographolide monosuccinate

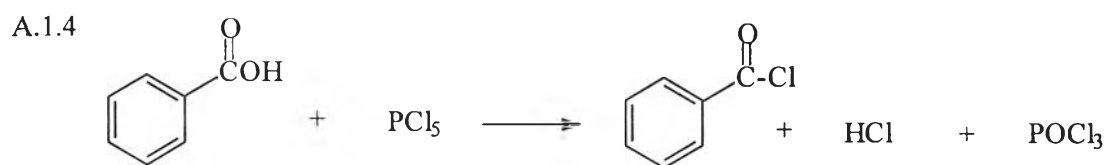
Figure 4. The chemical structures of Andrographolide and related diterpene lactone synthesized compounds (continued )

The synthesis of these compounds and seven related diterpene lactone synthesized in this experiment, based on many general methods of synthesis including the synthesis of Acyl halide, Ester. General methods for the synthesis were described as below (Solomons, 1984; Morrison and Boyd.1987 ; Furniss et al.1991).

#### 4.1 Synthesis of acyl halide

##### A.1 The use of carboxylic acid.

The conversion of carboxylic acid into the corresponding acyl chloride is usually achieved by heating the acid with phosphorus tri-chloride, or phosphorus pentachloride or thionyl chloride (See Scheme1-A.1.1, A.1.2,A.1.3 ) The acid chloride was formed in good yield. Phosphorus pentachloride is the preferred chlorinating agent for aromatic acid which contain electron withdrawing substituents, and do not react readily with thionyl chloride (See Scheme1-A1.4 ).



Scheme 1. The synthesis of Acyl halide.

A. The used of carboxylic acids.

## 4.2 Synthesis of esters.

### A. Direct esterification for aliphatic and aromatic carboxylic acid.

The interaction between a carboxylic and an alcohol is a reversible process and proceeds very slowly. Equilibrium is only attained after refluxing for several days. If, however, about 3 percent of either concentrated sulfuric acid or dry hydrogen chloride is added to the mixture, the same point of equilibrium can be reached after a few hours. When equimolecular quantities of the acid and alcohol are employed, only about two-thirds of the theoretically possible yield of ester is obtained (See Scheme 2-A).

The esterification reaction of alicyclic alcohols proceeds best when the alcohol is saturated with hydrogen chloride and treated with an excess of the carboxylic acid (The Fischer-Speier method); very impure ester results if sulfuric acid is used as the catalyst.

The process of acid-catalysed esterification in the presence of benzene, or, better, of toluene, is greatly facilitated if the water produced in the reaction is removed by distillation as an azeotrope (See Scheme 2-A.2).

### B. Esters from acid chloride

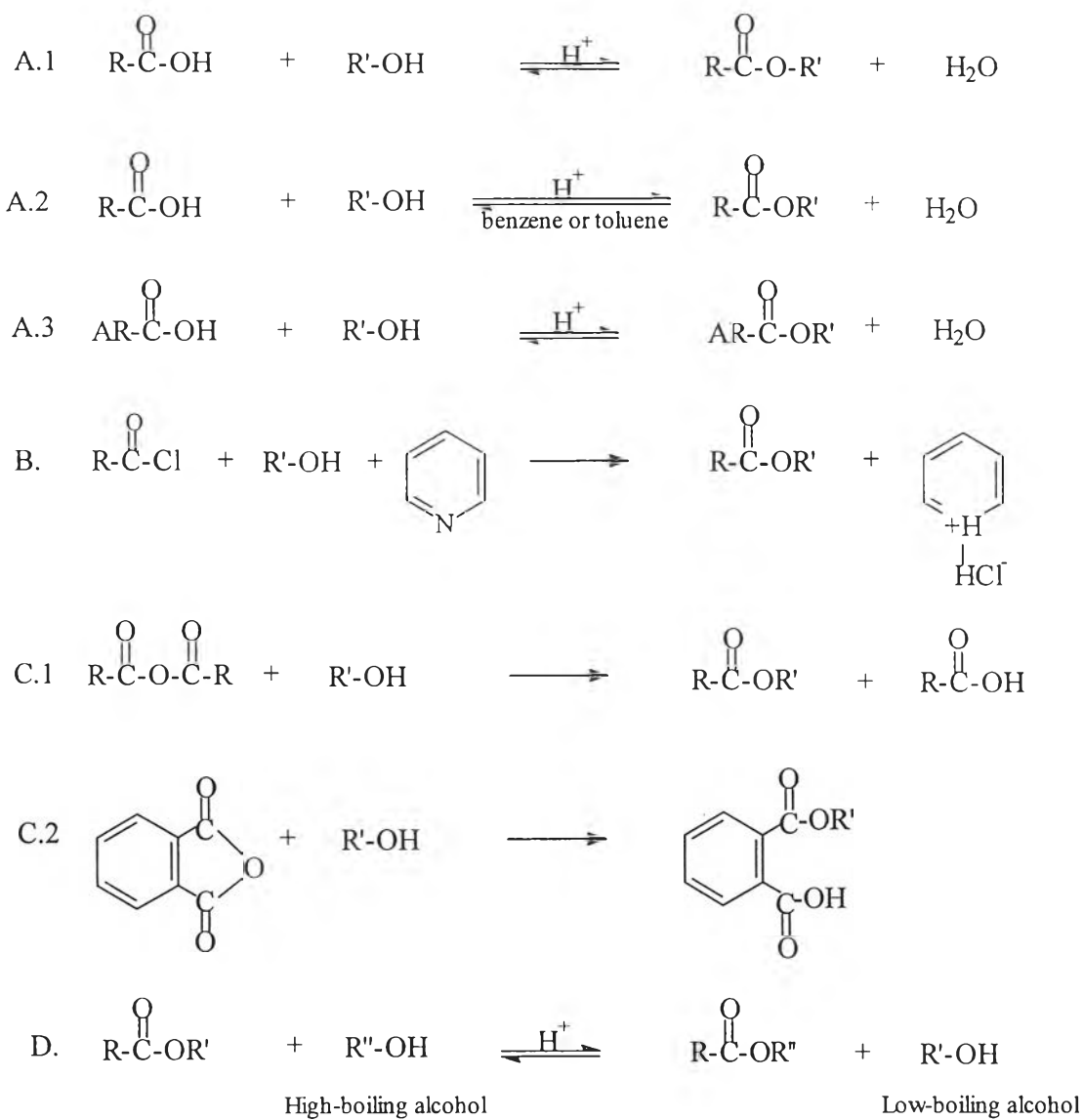
Esters can also be synthesized by the reaction of acid chlorides with alcohols. Since acid chlorides are much more reactive toward nucleophilic substitution than carboxylic acids, the reaction of an acid chloride and an alcohol occurs rapidly and does not require an acid catalyst. Pyridine is usually added to the reaction mixture to react with the hydrogen chloride that is formed (See Scheme 2-B).

### C. Esters from acid anhydrides.

Acid anhydrides also react with alcohol to form esters (See Scheme 2-C.1). Cyclic anhydrides react with one mole of an alcohol to form a compound that is both an ester and an acid (See Scheme 2-C.2).

### D. Transesterification

Esters can also be synthesized by transesterification. The mechanism for transesterification is similar to that for an acid-catalysed (or an acid-catalyzed ester hydrolysis) (See Scheme 2-D). In this procedure the equilibrium of the reaction was shifted to the right by allowing the low-boiling alcohol to distill from the reaction mixture.



Scheme 2. The synthesis of esters.

- A. Direct esterification for aliphatic and aromatic carboxylic acids.
- B. Esters from acid chlorides
- C. Esters from acid anhydrides
- D. Transesterification